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Malaysia [15], 8 weeks in Ghana [5] and 5 weeks in Botswana [14], but longer than that in other studies [8,16]. As reported elsewhere [9,12], the results indicated that the institutional delay was more significant than delays in diagnosis and treatment. The most common reasons for a doctor's delay were a low index of suspicion for tuberculosis on the part of physicians and healthcare system, as well as laboratory delays and the distance to a hospital. Previous studies have reported similar findings, and have also identified under-utilised chest X-ray examination facilities and a failure to perform sputum smear examinations as important reasons for a doctor's delay [11,12,14,16,17].

In conclusion, delays in diagnosis and treatment of pulmonary tuberculosis were a common problem at the Heybeliada Center for Chest Disease and Thoracic Surgery. Delayed diagnosis results in a more advanced disease state, the likelihood of complications, increased mortality, and enhanced transmission of infection among healthcare workers and in the community. Delays should be reduced for good control of tuberculosis. Education of physicians and the public about tuberculosis, reductions in healthcare system and laboratory delays, together with improvements in economic status and sociocultural factors, are the most important factors likely to reduce delays in diagnosis and treatment among tuberculosis patients.

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RESEARCH NOTE

Monitoring of vancomycin serum levels for the treatment of staphylococcal infections

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ABSTRACT

Vancomycin serum concentrations were determined for 1737 patients treated with either 2 × 1 g of vancomycin or 4 × 500 mg daily (780 patients), according to current nomograms, or by

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continuous infusion (957 patients) with a loading dose (1 g) and a total of 2–6 g daily. Trough serum concentrations were determined after 36–48 h. Adequate serum levels for the treatment of a normal methicillin-resistant *Staphylococcus aureus* (MRSA) and a glycopeptide-intermediate *S. aureus* (GISA) were observed in 81% and 20.9% of patients, respectively. The data support theoretical arguments that higher and more sustained serum levels of vancomycin, obtained by continuous infusion, may enhance clinical efficacy.

Keywords Continuous infusion, GISA, MRSA, serum concentration, vancomycin

Original Submission: 19 May 2005; **Revised Submission:** 13 June 2005; **Accepted:** 9 July 2005

Clin Microbiol Infect 2005; 12: 92–95
10.1111/j.1469-0691.2005.01306.x

More than 45 years after the introduction of vancomycin for the treatment of severe antibiotic-resistant staphylococcal infections, there are still controversies regarding the determination and interpretation of vancomycin serum concentrations [1–7]. Older studies focused on toxicity without considering clinical efficacy [8–11]. When performed and reported, serum assays always involved very few patients and the interpretation of the results was debatable. The aims of the present study were to determine the trough vancomycin serum concentrations in a large number of patients, and to consider the rationale for modifying the currently recommended 'acceptable therapeutic range', taking into account the pharmacokinetics, toxicity and antibacterial activity of vancomycin in combination with the clinical results.

Serum assays are performed routinely in the Hospital Saint Joseph, Paris, for all patients receiving vancomycin therapy. In total, 1737 patients treated during 1998–2004 were enrolled in the study. The patients received either 1 g of vancomycin every 12 h, or 500 mg every 6 h (according to current nomograms), or were treated by continuous infusion with a loading dose (1 g) and a total daily dose of 2–6 g. The daily dose was then adapted after further monitoring. The first trough serum assays were performed at steady state after treatment for 36–48 h; 5–10 mL of blood was drawn from the controlateral vein, and assays were performed within 1 h by the fluorescence polarisation immunoassay (TDx; Abbott Diagnostics, Rungis, France). The results are presented in Table 1.

Table 1. Trough vancomycin serum levels (first assay only) obtained in 1737 patients after either 2–4 separate doses (n = 780) or administration by continuous infusion (n = 957)

Serum level (mg/L)	No. patients with the indicated serum level[a]	
	2–4 separate doses	Continuous infusion
<5	148 (19.0%)	15
5–10	204	60 (7.9%)
10–15	160	212
15–20	103	173
20–25	70 (68.8%)	176
25–30	35	121 (71.2%)
30–35	22	74
35–40	12	59
>40	26 (12.2%)	67 (20.9%)

[a]Dialysed patients excluded.

When the 'Mississippi mud' was released during the 1950s, it contained impurities responsible for renal and ototoxicity or allergic reactions [8–11]. Cases of toxicity occurred during the first 10 years of vancomycin use, often in patients receiving other nephrotoxic compounds, or who had pre-existing renal dysfunctions. In the present study, <1% of the 1737 patients treated during the 7-year period of the study with trough concentrations ≤40 mg/L suffered from vancomycin-related toxicity (N. Desplaces and A. Ben Ali, personal communications). Vancomycin has a narrow spectrum of activity, restricted to most Gram-positive bacteria, and is the drug of choice for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). The vancomycin MIC for MRSA is 1–2 mg/L for fully vancomycin-susceptible strains. All strains with MICs ≥ 4 mg/L can be considered to be (hetero) glycopeptide-intermediate *S. aureus* (GISA) on the basis of population analysis profiles [12,13].

Vancomycin inhibits peptidoglycan synthesis by binding to the D-Ala-D-Ala terminus of the nascent murein monomer, resulting in the inhibition of cell-wall synthesis. Only 50% of the vancomycin arriving at the surface of a staphylococcus will reach the target site. GISA are characterised by a thicker cell-wall with increased amounts of peptidoglycan, and the increased quantities of unprocessed D-Ala-D-Ala cause

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increased 'trapping' and 'clogging', resulting in higher vancomycin MICs and the increased inoculum effect observed with GISA in comparison with fully vancomycin-susceptible strains [12–15]. This can explain the therapeutic failures observed in the treatment of GISA infections, where a concentration of 8–16 mg/L is required at the site of infection in order to totally inhibit large numbers of bacteria (10^8 CFU/g), in contrast to 3–4 mg/L for a fully vancomycin-susceptible strain [12–14]. Continuous infusion increases diffusion of vancomycin in body fluids and tissues, with the result that a more sustained concentration is achieved more quickly.

The 'therapeutic range' for vancomycin was established in the early 1980s in four healthy subjects who each received 500 mg of vancomycin, yielding peak concentrations of 20–40 mg/L and trough concentrations of 5–10 mg/L, obviously without any clinical correlation [13]. Vancomycin is 50% protein-bound in serum, which explains the 2–4-fold MIC increase *in vivo* and the occurrence of breakthrough positive blood-cultures, particularly in patients infected with GISA strains [12–15]. The tissue concentration of vancomycin does not exceed 30–40% of the serum concentration [13]. Other important factors to be considered include the decreased in-vivo bactericidal activity, the inoculum effect, the attachment of staphylococci to foreign bodies, and the production of biofilm. A trough vancomycin serum level of 15–25 mg/L is mandatory for the treatment of a fully glycopeptide-susceptible MRSA, with 30–40 mg/L (administered by continuous infusion) being required for treatment of a GISA infection [12,16]. In the present study of 1737 patients who were treated either conventionally or with continuous infusion, 19% and 7.9%, respectively, of those infected with a fully vancomycin-susceptible *S. aureus*, and 87.8% and 79.1%, respectively, of those infected with a GISA isolate failed to receive an adequate dose. Similarly, a study of paediatric patients reported that <20% had adequate therapeutic serum levels [6]. Theoretical aspects, often unfounded and misinterpreted, such as nomograms based solely on creatinine clearance, are likely to be inaccurate for some patients [7]. Other practical considerations, including cost, should not counterbalance the risk to the patient and the consequences of inadequate treatment [1].

Several previous reports have claimed that clinical cure does not always correlate with vancomycin serum concentrations [2,3], and no clinical cure attributed to vancomycin can be expected if the serum concentration remains below the MIC, particularly in the case of GISA. Sabath [14] reported that up to 6 g vancomycin/day were required to eliminate strains that, from the increase in MICs observed with a heavy inoculum (from 2 to 32–64 mg/L), were probably GISA. Nomograms are necessary, but monitoring is essential for dose adjustment and follow-up. The data presented above strengthen the theoretical arguments that higher and more sustained serum levels, obtained by continuous infusion, may contribute to a better clinical efficacy.

Some investigators have suggested that determination of vancomycin serum concentrations is unnecessary until the relationship between serum concentration and clinical outcome has been demonstrated [2]. However, after waiting for such results for more than 30 years, it seems appropriate to continue monitoring vancomycin serum levels in order to ensure effective therapeutic concentrations until the results of well-designed clinical studies become available.

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